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SPECIFICATION

1. Title of the Invention

POROUS CERAMIC IMPREGNATED WITH DRUG SOLUTION

2. Claims

1) A porous ceramic impregnated with a drug solution characterized in that the porous ceramic comprises pores of 10 to 500 μm in diameter, the pores communicated with the exterior at least on the surface and impregnated with an anticancer agent and/or an antibiotic.

2) The porous ceramic impregnated with a drug solution according to claim 1, characterized in that the porous ceramic is a porous sintered body composed of, as a main component, one or a mixture of two or more of calcium phosphate, alumina, zirconia, and silicon nitride.

3) The porous ceramic impregnated with a drug solution according to claim 2, characterized in that the calcium phosphate is hydroxyapatite or tricalcium phosphate.

4) The porous ceramic impregnated with a drug solution according to any one of claims 1 to 3, characterized in that the porous ceramic is a hollow body.

3. Detailed Description of the Invention

The present invention relates to a drug vessel for treating osteomyelitis and malignant tumors by being embedded in the affected area of a living body.

In a conventional method, which has been employed to treat the affected area of osteomyelitis, a vinyl tube is inserted in a suppurating area, and then, an antibiotic is fed into the suppurating area through the vinyl tube to wash it. However, this method only tentatively washes the suppurating area, so that the antibiotic cannot be delivered over the entire suppurating area and remain there over a long period. As a result, this method has a drawback in that the treatment is performed but incomplete.

The present invention was made to improve this and is directed to provide porous ceramic impregnated with a drug solution characterized in that the porous ceramic comprises pores of 10 to 500 μm in diameter communicated with the exterior at least on the surface, is composed of, as a main component, one or a mixture of two or more of calcium phosphate, alumina, zirconia, and silicon nitride, and is impregnated with a drug. The porous ceramic has the following advantages.

First, since the porous body is impregnated with a drug, the drug permeates into the affected area over a long period, improving the efficiency of treatment.

Second, since the drug vessel is made of ceramics harmless to a living body, if it is left in the living body, no problem is raised. In particular, calcium phosphate is quite advantageous because it facilitates formation of a bone. It fills up a lost part of bone simultaneously with treatment.

The diameter of the pores herein is specified as 10 to 500 μm. This is because when the pore diameter is 10 μm or less, an elution rate of a drug is slow, with the result that a long time is required for treatment; on the other hand, when the pore diameter is 500 μm or more, the elution rate of a drug is too fast, with the result that the period is too short and insufficient to apply effective treatment.

Furthermore, as porous ceramic, any material may be used as long as it is harmless to a living body as mentioned above. Calcium phosphate (such as hydroxyapatite, tricalcium silicate), alumina, zirconia, and silicon nitride as mentioned above are most suitable since they have high mechanical strength and manufactured at reasonable cost. Furthermore, if the porous ceramic is a hollow body, it is easily handled since a drug can be injected through the hollow body. Even if the porous ceramic is not a hollow body, the porous ceramic may be impregnated with a drug in vacuum or the like. The hollow body may have a bottom or not.

Next, a method of manufacturing the porous ceramic will be explained. First, an organic substance or a binding agent such as clay is added in an appropriate amount to an appropriate ceramic powder mixture of 10 to 500 μm in diameter. Then, the mixture is molded by an appropriate method such as press, extrusion, and green body press, followed by sintering. The sintering is preferably stopped in the state where the porous body still has open pores before the open pores are completely closed and still has appropriate strength. If the entire pores are closed, the effect of the present invention cannot be produced. Pores are allowed to remain after sintering by another method, in which powder (10 to 500 μm in diameter) of carbon or an organic substance, which will be baked off during a sintering process is added to ceramics

powder. There is still another method of forming pores of 500 μm or less in the formed body or the sintered body formed in accordance with either one of the aforementioned two methods by a drill. Thereafter, the formed body, after it is sintered, and the sintered body, as it is, are used as a drug vessel.

Now, the present invention will be explained in more detail by way of Examples.

Example 1

To hydroxyapatite of 30 μm in average diameter, 3% of gum arabic was added. The mixture was molded into a cylindrical form with a bottom, having an outer diameter of 5 mm, an inner diameter of 3 mm, a length of 15 mm, a thickness of 1 mm, and then sintered at 1000°C in the air to obtain a cylindrical porous body. The pores formed on the surface of the porous body had an average diameter of 20 μm, an outer diameter of 4.2 mm, an inner diameter of 2.5 mm, a length of 13 mm, and a thickness of 0.8 mm. The pores were impregnated with an antibiotic, cephalosporin, by introducing it through the hollow portion. A porous ceramic impregnated with a drug was embedded in the thighbone of rabbits. The concentration of the antibiotic in the bone marrow of the thighbone was measured by killing the rabbits one by one.

As a result, values of the antibiotic concentration within the bone marrow were constant. It was confirmed that the effect of the antibiotic of single injection lasts for about 2 weeks. In addition, the peripheral osteogenesis of the injection portion was extremely favorable.

On the other hand, cephalosporin was introduced into the thighbone of rabbits through a vinyl chloride pipe in the same manner as in Example 1 and washed in accordance with a conventional example. In

this case, values of the cephalosporin concentration in the bone marrow were not constant.

Example 2

A partially stabilized zirconia containing alumina, which contained tricalcium phosphate, MgO, and SiO_2, whose average particle sizes are shown in Table 1, in an amount of 5% by weight (hereinafter "by weight" is omitted) and 5% of Y_2O_3, and α-Si_3N_4 containing 10% of Y_2O_3 were prepared, separately. To each of the mixtures, 3% of methacrylic acid and isobutyl ester, 1% of nitrocellulose, and 0.5% of dioctylphthalate were added, and further trichloroethylene and n-butanol were added as solvents to prepare a green sheet of 1 mm thick. Through-holes having the diameter shown in Table 1 were formed by a drill at intervals of 0.96 mm to 1.2 mm. The green sheet was cut into pieces of 20mm width and 23mm long and rolled to form cylinders having an outer diameter of 6 mm and a length of 23 mm, which were then sintered up to the temperature shown in Table 1. The average porosities of them is also listed in Table 1. An antibiotic was injected in the same manner as in Example 1. As a result, values of the concentration of the antibiotic in the bone marrow are constant compared to a conventional case where a drug solution was injected through a vinyl chloride pipe embedded in the thighbone of a rabbit. In addition, the peripheral osteogenesis was extremely favorable.

Table 1

Main component	Average particle size of raw material (μm)	Average pore size before sintering (μm)	Pitch (mm)	Sintering temperature (°C)	Sintered product (μm)
Tricalcium phosphate	10	100	0.9	1200	80

Alumina	3	200	1.0	1600	160
Zirconia	0.5	300	1.3	1500	250
Silicon nitride	1	400	1.5	1650	340

In the present invention, since porous ceramic containing a drug (solution) is embedded in a living body over a long period as mentioned above, the drug solution can be dispersed in an affected area at an optimal rate. In this manner, an efficient therapeutic effect can be obtained. The above Examples are described taking a cylindrical form as an example; however, the present invention is not limited to this example. A rectangular column, pyramid, and cone, which may have a bottom or not, and may be not hollow may be effective. Besides these, spherical shape, egg-shaped, spindle shape, etc. may be effective. The shape of the porous body may be appropriately determined depending upon the portion of a living body in which the porous body is to be embedded.

The porous body may be satisfactory as long as it has pores at least on the surface. Pores of 10 to 500 μm are not necessary present throughout the entire part of the porous body. The pores must communicate with the exterior. No effect is produced if the surface of pores is closed.

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⑭薬液含浸多孔質セラミックス

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明　細　書

1.発明の名称

薬液含浸多孔質セラミックス

2.特許請求の範囲

1）孔径10～500μmの外部に連通する気孔を少なくとも表面に有し、該気孔内に制ガン剤及び／又は抗生物質を含浸せしめられていることを特徴とする薬液含浸多孔質セラミックス。

2）多孔質セラミックスが、リン酸カルシウム塩，アルミナ，ジルコニア，窒化珪素の1種又は2種以上の混合物を主成分とする多孔質焼結体である特許請求の範囲第1項記載の薬液含浸多孔質セラミックス。

3）リン酸カルシウム塩が水酸アパタイト又はトリカルシウムフォスフェートである特許請求の範囲第2項記載の薬液含浸多孔質セラミックス。

4）多孔質セラミックスが中空体である特許請求の範囲第1項～第3項のいずれかに記載の薬液含浸多孔質セラミックス。

3.発明の詳細な説明

本発明は、生体の骨髄炎，悪性腫瘍の患部に埋入し治療する薬物容器に関するものである。

従来骨髄炎の患部を治療するには、ビニールチューブを化膿部分に通し、ビニールチューブを通して抗生物質を送り込み洗浄する方法が採用されてきたが、一時的の洗浄に過ぎないため、抗生物質が長期間化膿部全体にゆきわたらず、従って治癒が不完全となる問題があった。

本発明はこれを改良するためになされたもので孔径10～500μmの外部に連通する気孔を少なくとも表面にもち、リン酸カルシウム塩，アルミナ，ジルコニア，窒化珪素等の1種又は2種以上の混合物を主成分とする多孔質セラミックスの気孔内に、薬物を含浸せしめたことを特徴とする薬物含浸多孔質セラミックスを提供するもので下記の如き長所を有している。

第一に多孔質体の中に薬物を含浸せしめたものであるから、薬物は長期間にわたって患部へ染み出し、有効に治療効果を上げる。

第二に薬物容器は生体に為害性のないセラミックスであるため、生体内に残っても、何ら問題が残らない。特にリン酸カルシウム塩は骨形成が容易であるため、治癒と共に骨の欠損部の代用となり、非常に好都合となる。

ここで気孔の孔径を10～500μmとした理由は、10μm以下では薬物の溶出速度が遅く治療に長期間を要し、一方500μm以上では、薬物の溶出速度が速過ぎて治療効果が短期に尽き、不十分となる。

又多孔質セラミックスは上記の如く生体に為害性がないものなら、何れの材質でもよいが、上記のリン酸カルシウム塩（水酸アパタイトやトリカルシウムシリケート等），アルミナ，ジルコニア，窒化珪素等は機械強度も高く、製造費も適当なため最も適したものである。更に多孔質セラミックスが中空体であれば、この中空体を通して薬物を注入することができるので、操作が容易であるが、中空体でない場合は真空中で浸透含浸させる等の方法をとることができる。中空体は有底、無底何れでもよい。

次にその製造法の1例を述べれば、先ずセラミック粉末の10～500μmの粒径の適当な混合物に有機質、又は粘土等の結合剤の適当量を加え、プレス，押出し，坏土プレス等適宜な方法で成形し、焼成することによって得られるが、焼成は完全に気孔を閉鎖する以前の開口気孔を有する状態で且つ適当な強度を有する状態で止めることが好ましく、全体がすべて閉鎖気孔になっては本発明の作用効果が失われる。又別の方法としてはセラミック粉末に炭素、有機物等の焼成中、焼失する物質の10～500μmの粉末を混ぜることにより、焼成後気泡を残すことができる。又更に一つの方法としては、上記2種の方法で成形した成形体又は焼結体に直径500μm以下のドリルで孔をあけた後、成形体ならば焼成し、焼結体ならばそのまま薬物容器とすることができる。

以下の実施例によって一層具体的に説明する。

実施例1

平均粒径30μmの水酸アパタイトにアラビアゴム3％を加え、ラバープレスにより外径5㎜内径3㎜、長さ15㎜、肉厚1㎜の有底の円筒状に成形し、大気中で1000℃に焼成し、円筒状の多孔質体とした。この多孔質体の表面平均気孔サイズは20μmで外径4．2㎜，内径2．5㎜，長さ13㎜，肉厚0．8㎜であった。この中空部より、セファロスポリンを注入し、気孔中に抗生物質を含浸せしめた。この薬液含浸多孔質セラミックスを兎の大腿骨に埋入し、継続的に屠殺して、大腿骨髄内の抗生物質濃度を測定した。

この結果、骨髄内の抗生物質濃度は一定した値を示し、1回の投与において、約2週間持続することを認めた。又この際周囲の骨形成は極めて良好であった。

一方従来法として塩化ビニールパイプを用いて実施例1と同様に兎の大腿骨部にセファロスポリンを注入洗浄したが、その際の骨髄内の濃度は一定した値が得られなかった。

実施例2

第1表に示す平均粒径のトリカルシウムフォスフェート，MgO，SiO_2 を各5重量％（以下「重量」を省く）を含むアルミナ，Y_2O_3 5％を含む部分安定化ジルコニア，Y_2O_3 10％を含むα－Si_3N_4 をそれぞれ調整し、メタクリル酸，イソブチルエステル3％，ニトロセルローズ1％，ジオクチルフタレート0．5％を加え更に溶媒として、トリクロールエチレン，n－ブタノールを加えて厚さ1㎜のグリーンシートに作り、第1表に示す直径の孔をドリルにてピッチ0.96㎜～1.2㎜の間隔でスルーホールに形成し、巾20㎜，長さ23㎜に切断して丸めて、外径6㎜，長さ23㎜の円筒状に成形し第1表に示す温度に焼成した。その平均気孔率を第1表に併記する。これに実施例1と同様にして抗生物質を注入し、兎の大腿骨内に埋入した従来法の塩化ビニールパイプより薬液を注入洗浄する場合に比較し、骨髄内の抗生物質濃度は一定した値を示し、又周囲の骨形成は極めて良好であった。

第　1　表

主成分	原料平均粒径（μm）	焼成前気孔径（μm）	ピッチ（mm）	焼成温度（℃）	焼成物（μm）
トリカルシウムフォスフェート	10	100	0.9	1200	80
アルミナ	3	200	1.0	1600	160
ジルコニア	0.5	300	1.3	1500	250
窒化珪素	1	400	1.5	1650	340

本発明は上記の如く、長期間にわたって生体内に薬物を含む多孔質セラミックスが埋入されるため、薬液は最適の速度で患部へ拡散し、有効に治療効果を上げるものである。尚本実施例では、円筒形状を例に述べたが、本発明はこれにこだわることなく、角柱、角錐、円錐の有底又は無底又は中空部なしの形状の他、球形、卵形、紡錘形等何れの形状でも有効なもので、その形状は生体の埋入れ個所に応じて、適宜決定されるものである。

又気孔も少なく表裏面に有しておればよく、必ずしも、全部分が１０～５００μｍの気孔を有する必要はないものであるが、外部に連通する気孔であることが必要で表面を閉鎖された気孔では効果が無いものである。